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Family history as a co-factor for adenocarcinoma and squamous cell carcinoma of the uterine cervix: Results from two studies conducted in Costa Rica and the United States

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Previous work suggests that cervical cancer may aggregate in families. We evaluated the association between a family history of gynecological tumors and risk of squamous cell and adenocarcinomas of the cervix in 2 studies conducted in Costa Rica and the United States. The Costa Rican study consisted of 2,073 women (85 diagnosed with CIN3 or cancer, 55 diagnosed with CIN2 and 1,933 controls) selected from a population-based study of 10,049 women. The U.S. study consisted of 570 women (124 with *in situ* or invasive adenocarcinomas, 139 with *in situ* or invasive squamous cell carcinomas of the cervix and 307 community-based controls) recruited as part of a multicentric case-control study in the eastern part of the United States. Information on family history of cervical and other cancers among first-degree relatives was ascertained *via* questionnaire. Information on other risk factors for cervical cancer was obtained *via* questionnaire. Human papillomavirus (HPV) exposure was assessed in both studies using broad spectrum HPV L1-based PCR testing of exfoliated cervicovaginal cells and in Costa Rica by additional testing of plasma collected from participants for antibodies against the L1 protein of HPV types 16, 18, 31 and 45 by ELISA. A family history of cervical cancer in a first-degree relative was associated with increased risk of squamous tumors in both studies (odds ration [OR] = 3.2 for CIN3/cancer *vs.* controls; 95% confidence interval [CI] = 1.1–9.4 in Costa Rica; OR = 2.6 for *in situ*/invasive squamous cell carcinoma cases *vs.* controls, 95% CI = 1.1–6.4 in the Eastern United States study). These associations were evident regardless of whether the affected relative was a mother, sister or daughter of the study participant. Furthermore, observed effects were not strongly modified by age. In Costa Rica, the effect persisted in analysis restricted to HPV-exposed individuals (OR = 3.0; 95% CI = 1.0–9.0), whereas in the Eastern United States study there was evidence of attenuation of risk in analysis of squamous carcinoma cases restricted to HPV positive women (OR = 1.4; 95% CI = 0.29–6.6). No significant association was observed between a family history of cervical cancer in a first-degree relative and adenocarcinomas (OR = 1.3; 95% CI = 0.43–3.9). History of gynecological tumors other than cervical cancer in a first-degree relative was not significantly associated with risk of disease in either study. These results are consistent with a role of host factors in the pathogenesis of squamous cell cervical cancer, although familial aggregation due to shared environmental exposures cannot be ruled out.

Key words: cervical carcinoma; family history; human papillomavirus; susceptibility

Cervical cancer is caused by infection with one of about 15 oncogenic types of human papillomavirus (HPV).[1] Although HPV are common sexually transmitted infections, cervical cancer and its immediate precursors are uncommon. Various co-factors have been postulated to be important determinants of disease risk among HPV infected individuals. Well-established exogenous co-factors associated with the development of cervical cancer include HPV type and variants, age, smoking, high parity and long-term oral contraceptive use.[2] Infection with other sexually transmitted agents such as herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis*,[3,4] and some nutritional factors might also be associated with risk of disease.[5]

Familial aggregation of cervical cancer has been reported in the literature from record linkage studies in Scandinavia and the United States.[6] These studies suggest that a family history of cervical cancer increases risk of disease. Because familial aggregation could be a result of genetic predisposition among family members or shared environmental exposures and lifestyle factors, it is not known currently whether the aggregation observed for cervical cancer is due to genetic or environmental effects. In support of an underlying genetic explanation for the observed familial aggregation, however, one study observed stronger effects of family history when biological mothers/sisters were evaluated compared to half-sisters and non-biological (*i.e.*, adopted) relatives.[7] Studies have reproducibly shown associations between human leukocyte antigen (HLA) alleles and risk of cervical cancer and pre-cancer, further supporting the role of inherited genetic factors in the etiology of this disease.[8]

Most studies of cervical cancer and pre-cancer that have evaluated the role of family history have focused on squamous cell carcinomas because this histological form of cervical cancer comprises the vast majority of cervical tumors diagnosed each year.[9] In contrast to squamous cell carcinomas of the cervix, the association between family history of cancer and risk of cervical adenocarcinomas and adenosquamous carcinomas (tumors with mixed squamous and glandular components) has been studied infrequently. Infection with oncogenic HPV have been shown to be necessary for the development of both adenocarcinomas

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and adenosquamous carcinomas of the uterine cervix, but the distribution of HPV types and variants in these tumors vary from those seen in the more common squamous cell cancers.[10] The cofactors associated with these glandular tumors have been shown to vary from those identified for squamous cell tumors.[11] It is unclear whether family history of cervical or other cancers is associated with risk of subsequent development of cervical adenocarcinomas and adenosquamous carcinomas, although limited evidence does exist in support of such an association.[12]

As a starting point for our efforts to evaluate the role of genetic susceptibility in the development of cervical cancer, we sought to evaluate whether family history of cervical or other cancers is associated with cervical cancer of squamous or glandular origin. For this purpose, data from 2 large studies were evaluated: a case-control study of squamous cervical cancers and its precursors nested within a population-based cohort of 10,000 women in Costa Rica,[13] and a multicenter case-control study of *in situ* and invasive squamous and adenocarcinomas conducted in the United States.[11]

Material and methods

Costa Rican Cohort Study

As described previously, a 10,000-woman population-based cohort was established in Guanacaste, Costa Rica in 1993–4 to study the natural history of HPV and the origins of cervical intraepithelial neoplasia (CIN) type 3 and cervical cancer.[13,14]

Data for the present analyses were derived from 3 components of the Costa Rican cohort study: an initial screening visit (Visit 1), a colposcopy referral visit for participants with an indication of abnormalities and for a random sample of the study population (Visit 2) and a home visit to collect more complete pedigree and family history of cancer information for the subset of participants who reported a family history of gynecological cancers in a first-degree relative (Visit 3), as described below.

At the initial screening visit (Visit 1), participants responded to a risk factor questionnaire. Sexually active women underwent a pelvic examination, at which time various specimens were collected to permit visual, cytological and viral DNA testing by hybrid capture and PCR, as described previously.[13,15,16] Plasma obtained from blood was tested for antibodies against HPV16, HPV18, HPV31 and HPV45 by ELISA, as described previously.[17]

Women with cervical abnormalities (equivocal or more severe results) at the time of the enrollment pelvic exam by visual inspection, cytology or cervicography, or who were in a 2% random sample of the population were referred to colposcopy (Visit 2), at which time a more detailed questionnaire was administered that obtained additional information on cervical cancer risk factors, including family history of gynecologic cancers among first-degree female relatives. To limit possible effects of recall bias, this questionnaire was administered before the colposcopy evaluation, at a time when participants were still unaware of their diagnosis. For women who responded positively to the question on whether they had a family history of gynecological cancer, questions were asked regarding the type of gynecological cancer and the specific first-degree relative affected.

At the colposcopy visit, visible lesions were biopsied. Based on review of cytology, cervigram and histology, each woman was assigned a diagnosis. A single pathologist (MES) reviewed diagnostic material to establish a final study diagnosis.[18] This final diagnosis was defined based on histology or cytology when cytological results were confirmed by more than one method of evaluation. All cancers and 93% of all high-grade diagnoses were defined histologically. For women diagnosed with high-grade disease, materials were re-reviewed by a second United States pathologist (T.C. Wright, NY, NY), who distinguished CIN2 from CIN3 lesions.

For women who reported a positive family history of gynecological cancer among a first-degree family member, a follow-up visit to the participant's home was attempted by trained staff to obtain more complete family history and pedigree information (Visit 3), using a questionnaire adapted from those used to ascertain family history in genetic studies of multiplex cancer families. In this questionnaire, information was collected on total number of first-, second-, and third-degree relatives by relationship, family history of gynecological cancer was confirmed, and history of cancers at other sites among all reported male and female relatives was assessed.

Of the 10,049 women who agreed to visit one of our study clinics for an initial visit (Visit 1), 291 women refused or had physical problems that prevented a pelvic exam, 610 women reported having a hysterectomy in which the cervix was removed and 583 were self-reported virgins in whom pelvic examinations were not carried out. These women were excluded from the present study (8-565 participants remaining after these exclusions were made).

Our present study is further restricted to the 2,073 women who were referred to colposcopy, because only this subset of our cohort participants were administered the questionnaire that included questions on family history of gynecological cancer among first-degree relatives. Of 2,073 women, 12 were diagnosed with cervical cancer, 73 had a final diagnosis of CIN3, 55 had a final diagnosis of CIN2 and the remaining 1,933 participants were found to have low-grade lesions ($n = 179$), equivocal lesions ($n = 699$) or to be cytologically normal upon re-evaluation ($n = 1,055$).

Of the 2,073 participants seen in colposcopy (Visit 2), 116 (2 cancer, 8 CIN3, 3 CIN2 and 103 <CIN2) reported a family history of gynecological cancer among a first-degree relative and were targeted for a home visit (Visit 3). Home visits were successfully completed for 12 women with CIN2+ (92%) and 60 women with <CIN2 (58.3%). Limitation in study staff time to perform the home visits during the busy enrollment period of our cohort study precluded the possibility of performing this visit for all women with <CIN2 diagnosis.

For the analysis, we classified women into 3 groups. The first group included the 12 women with screening detected invasive cancer and the 73 women with a final diagnosis of CIN3. The second group included the 55 women with a final diagnosis of CIN2. The third group included all remaining women initially referred to colposcopy but found upon further evaluation to have a final diagnosis of low-grade lesions, equivocal lesions or normal ($n = 1,933$). This last group was considered the control group in our analyses.

Women with CIN2 and CIN3 were evaluated separately because of the possibility that CIN2 is a heterogeneous diagnosis particularly prone to misclassification (*i.e.*, consisting of a mixture of true precancerous lesions and semi-acute HPV infections).

Comparison of our control group to participants who were not referred to colposcopy and therefore were excluded from the present analysis showed the expected differences between women with and without cytological evidence of abnormalities, but no differences that might have importantly biased our estimates of family history association away from the null. More specifically, the mean age of the controls for the present family study and participants not referred to colposcopy was 37.8 years and 41.4 years, respectively ($p < 0.001$). The percentage of women with a secondary education was 36.5% and 32.4%, respectively ($p < 0.001$). The mean number of sexual partners was 2.2 and 2.0, respectively ($p = 0.002$). Similar proportions of both groups reported ever smoking (10.4% and 10.2%, respectively; $p = 0.79$). 68.9% of the family study controls reported ever using oral contraceptives compared to 61.7% of women who were not referred to colposcopy ($p < 0.001$); among users the reported duration of use was similar (4.4 *vs.* 4.4 years, respectively). The mean number of pregnancies was also comparable in both groups (4.3 *vs.* 4.7, respectively; $p < 0.001$). 22.1% of the family study controls were positive for oncogenic HPV types compared to 8.4% of women who were not

referred to colposcopy ($p < 0.001$); figures for non-oncogenic HPV types were 15.6% and 13.4%, respectively ($p = 0.01$).

Eastern United States Study

The Eastern Unites States study was designed to assess the similarities and differences between adenocarcinomas (including adenocarcinomas *in situ*, pure invasive adenocarcinomas, invasive adenosquamous carcinomas and other invasive carcinomas with a glandular component) and squamous cell carcinomas (including *in situ* and invasive tumors).[11] Our study included women between the ages of 18–69 diagnosed with cervical cancer at 1 of 6 participating medical centers in the Eastern United States. All incident *in situ* or invasive, primary adenocarcinomas and other cervical carcinomas demonstrating glandular involvement during the study period were eligible. To confirm the accuracy of the initial pathological diagnosis obtained from each participating clinical center, a panel of 3 expert pathologists jointly reviewed pathological specimens retrieved specifically for this purpose. At the time of review, a consensus diagnosis was obtained for each case reviewed and established the study diagnosis. Eighty-eight percent of cases were successfully reviewed; pathology specimens were unavailable for panel review for the remaining 12%. For the 88% of cases reviewed by the expert panel, their review invariably confirmed the initial diagnosis reported from the clinical centers. For the remaining unreviewed cases the initial clinical center diagnosis was used as the final study diagnosis.

A second case group was comprised of women diagnosed with *in situ* or invasive squamous cell carcinoma (SCC) of the cervix. The same eligibility criteria were applied to this second case group as were applied to the adenocarcinomas. SCC cases were matched to adenocarcinoma cases at a 1:1 ratio. Squamous cases were matched to adenocarcinomas on study center, age at diagnosis, date of diagnosis and stage of disease at diagnosis (*in situ vs.* invasive). For SCC cases, the initial pathological diagnosis reported by the participating clinical centers was used as the final study diagnosis. Review of a 10% subset of SCC cases by our expert panel uniformly confirmed the accuracy of the clinical center diagnosis.

Control women consisted of women identified through random-digit dialing and matched to adenocarcinoma cases at a 2:1 ratio. Controls were matched to adenocarcinoma cases on age, ethnicity and telephone exchange. Controls who reported a previous hysterectomy were not eligible for study.

The final analytic group included a total of 124 adenocarcinomas, of which 33 were adenocarcinoma *in situ* and 91 were invasive adenocarcinomas (response rate = 66%), 139 SCC, including 48 carcinoma *in situ* and 91 invasive tumors (response rate = 54%) and 307 community controls (response rate = 76%).

All participants completed an in-person interview. Information on family history of any cancer among a first-degree relative was collected. For women who reported a positive family history of cancer, the type of cancer and type of relative was assessed. All reported exposures were truncated 12 months before the diagnosis date (for cases) or an equivalent date (for controls) to avoid collecting information on exposures that occurred after disease occurrence. Cervicovaginal cells were collected from cases and controls by clinician or self-administered sampling and used for HPV DNA testing by PGMY L1 primer PCR, as described previously.[19]

Statistical analysis

Both polytomous[20] and pairwise dichotomous unconditional logistic regression models[21] were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) when evaluating the association between a family history of cervical or other gynecological cancers among a first-degree relative and risk of disease. Findings were largely comparable and so only results from pairwise dichotomous unconditional logistic regression are presented in our report. This choice was made because in some instances polytomous regression could not be carried out due to zero cells in 1 of the 2 case groups. Also, for the Eastern United States study, conditional logistic regression was not used because this would have resulted in the loss of cases and controls without a matched pair, and also because the control group was matched to the adenocarcinoma case group but not directly to the SCC case group.

The following cervical cancer risk factors were evaluated as potential confounders of the family history-disease association: age, number of partners, smoking, oral contraceptive use, number of pregnancies, and number of Pap smears before our study. To evaluate the possibility of confounding by these factors, models were generated that included the family history variable of interest and each of the potential confounders. When examined in this manner, none of the potential confounders altered the OR estimate associated with family history by more than 15%. Unadjusted estimates of risk are therefore presented in the results that follow. Given the modest size of our 2 studies and the fact that family history of cancer is a low prevalence event, it was not possible for us to evaluate the possibility of confounding further, by creating models that adjusted for multiple potential confounding factors simultaneously.

The potential for effect modification by important factors was evaluated by stratification. Factors that were evaluated for potential effect modification include age and stage of disease (*in situ vs.* invasive). Heterogeneity between age strata was evaluated by including an interaction term in the logistic models. Heterogeneity between *in situ* and invasive cases in the Eastern United States study was evaluated by directly comparing adenocarcinoma to SCC cases in a logistic model (case–case comparison). Because HPV is a necessary cause of invasive cervical cancer and its precursor lesions, further analyses were conducted by stratification on HPV status. In these analyses, all cases were considered HPV exposed and controls were considered HPV exposed if they (*i*) tested positive for HPV DNA by PCR for one of the following oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 (adenocarcinoma and Costa Rican studies) or (*ii*) had a positive anti-HPV antibody ELISA test for HPV16, HPV18, HPV31 or HPV45, with the positivity cutoff defined as antibody levels that were 3 standard deviations above the mean among concurrently tested virginal women from our cohort (Costa Rican study only).

Differences in the age distribution and in the distribution of cancer sites among relatives were compared between study groups using the non-parametric Kruskal-Wallis test.[22] The distribution of cancer sites reported among relatives was evaluated for individual tumor sites other than gynecological tumors that were observed frequently enough to warrant evaluation (including stomach, colon and liver) and for categories of tumors grouped based on etiological similarities as follows: tumors linked to HPV (cervix, vagina, anus, head and neck and penis cancers), tumors associated with infectious agents (cervix, vagina, anus, head and neck, penis, liver and stomach cancers), tumors linked to smoking (lung, cervix, head and neck, pancreas and kidney cancers), and selected tumors that have a hormonal etiology (endometrium, breast and ovary cancers). Both the absolute number of relatives reported as having cancer and the proportion of total relatives reported as having cancer were evaluated.

Results

Costa Rican Cohort Study

Detailed descriptions of the characteristics of participants in the Costa Rican Cohort Study have been reported previously.[14,23] As summarized in Table I, a family history of gynecological cancer among a first-degree relative was associated with a 2.4-fold increased risk of CIN3/cancer (95% CI = 1.2–4.7); no association was evident for CIN2 (OR = 0.97; 95% CI = 0.30–3.2). The association with CIN3/cancer was strongest when a family history of cervical cancer among a first-degree relative was specifically evaluated (OR = 3.2; 95% CI = 1.1–9.4). Because no evidence for an

TABLE I – ASSOCIATION BETWEEN FAMILY HISTORY OF CERVICAL AND NON-CERVICAL GYNECOLOGICAL CANCERS AND CERVICAL NEOPLASIA[1]

Family history	Costa Rican Study							Eastern United States Study						
	Controls	CIN 2			CIN3/Cancer			Controls	Adenocarcinoma			Squamous Cell Carcinoma		
	n	*n*	OR	95% CI	*n*	OR	95% CI	*n*	*n*	OR	95% CI	*n*	OR	95% CI
No gyn cancer in a first-degree relative	1,830	52	1.0		75	1.0		280	108	1.0		117		
Any gyn cancer in a first-degree relative	103	3	0.97	0.30–3.2	10	2.4	1.2–4.7	20	12	1.6	0.74–3.3	16	1.9	0.96–3.8
Non-cervical gyn tumors in a first-degree relative	72	3	1.4	0.43–4.6	6	2.0	0.85–4.8	10	7	1.8	0.67–4.9	5	1.2	0.40–3.6
Cervical cancer in a first-degree relative	31	0	0	0	4	3.2	1.1–9.4	10	5	1.3	0.43–3.9	11	2.6	1.1–6.4

[1]Results from the population-based study in Costa Rica and the multicentric study in the Eastern United States.

TABLE II – ASSOCIATION BETWEEN FAMILY HISTORY OF GYNECOLOGICAL CANCER AND CIN3/CANCER IN COSTA RICA[1]

Family history	Controls	CIN3/Cancer		
	n	*n*	OR	95% CI
No family history of cervical cancer in a first-degree relative	1,894	81	1.0	
Family history of cervical cancer in a first-degree relative				
Mother	22	3	3.3	0.96–11
Sister	10	1	2.4	0.31–19
Daughter	0	0	—	—
Oncogenic HPV-exposed controls[2]				
No family history of cervical cancer in a first-degree relative	1219	81	1.0	
Family history of cervical cancer in a first-degree relative	21	4	3.0	1.0–9.0
Women 35 years or younger				
No family history of cervical cancer in a first-degree relative	954	42	1.0	
Family history of cervical cancer in a first-degree relative	17	2	2.8	0.62–12
Women older than 35 years				
No family history of cervical cancer in a first-degree relative	940	39	1.0	
Family history of cervical cancer in a first-degree relative	14	2	3.5	0.78–16

[1]Results from the Population-Based Study in Costa Rica.—[2]Defined as DNA positive for an oncogenic HPV or antibody positive for HPV16, 18, 31, or 45, as defined in Methods.

association between family history and CIN2 was observed, and because for CIN3/cancer the strongest association was observed for a family history of cervical cancer, subsequent analyses focused on the CIN3/cancer case group and evaluated risk associated with a family history of cervical cancer among first-degree relatives. Similar patterns were observed in analyses that evaluated risk associated with a family history of any gynecological cancer among first-degree relatives (data not shown).

Elevations in risk were observed regardless of whether history of cervical cancer was reported among a mother or sister (Table II). No occurrences of cervical cancer among daughters were reported in our study. In analyses restricted to all CIN3/cancer cases and HPV exposed controls (Table II), an elevation in risk was observed for women who reported a family history of cervical cancer among a first-degree relative (OR = 3.0; 95% CI = 1.0–9.0). In this analysis, controls were classified as HPV exposed if they tested positive for HPV DNA by one or more oncogenic HPV types or were positive by serology for HPV types 16, 18, 31 or 45 (using a positivity cutpoint of 3 standard deviations above the mean among concurrently tested virginal women from our cohort). Similar findings were observed when the definition of HPV positivity was modified to include a more specific definition of seropositivity (5 standard deviations above the mean among virginal women) (OR = 2.8; 95% CI = 0.95–8.5) or when HPV exposure among controls was determined based on the presence of oncogenic HPV DNA only (*i.e.*, without considering serology results) (OR = 2.6; 95% CI = 0.77–8.6). Elevations in risk associated with a family history of cervical cancer were observed for women who were 35 years of age or less (Table II; OR = 2.8; 95% CI = 0.62–12) and those who were older than 35 years (OR = 3.5; 95% CI = 0.78–16) (p for heterogeneity = 0.82).

CIN3 cases with a positive family history of cervical cancer had a median age of 43.5 years compared to 34 years for CIN3 cases without such a history ($p = 0.31$). The age at diagnosis of cancer cases could not be compared by family history status because none of the 12 cancer cases reported a family history of cervical cancer. The median ages of controls with and without a family history of cervical cancer were 32 and 35 years, respectively ($p = 0.59$).

For women included in our more extensive evaluation of pedigree and family history data (*i.e.*, the 72 women described in the Material and Methods as having Visit 3), we evaluated the distribution of cancer sites reported among relatives of CIN3/cancer cases and controls. No striking or significant differences were observed in the distribution of individual cancer sites or in the distribution of cancer sites grouped on the basis of etiology (HPV, infectious agents, smoking, or hormones, as described in the Material and Methods), regardless of whether the absolute number or the proportion of total relatives affected was evaluated (data not shown). We did note that for 4 controls and one CIN2 case, the family history of gynecological cancer among a first-degree relative reported at the time of the colposcopy visit was not confirmed by the participant at the time of the follow-up home visit. Family history reported at the time of the colposcopy visit was confirmed, however, for all CIN3/cancer cases.

Eastern United States Study

Detailed demographic characteristics were reported previously.[11] As summarized in Table I, a family history of gynecological tumors was associated with a marginally significant 1.9-fold increase in risk of SCC (95% CI = 0.96–3.8) and with a non-significant 1.6-fold increase in risk of adenocarcinoma (95% CI = 0.74–3.3). The association with SCC was strongest and statistically significant when a family history of cervical cancer among

TABLE III – ASSOCIATION BETWEEN FAMILY HISTORY OF GYNECOLOGICAL CANCER AND HISTOLOGICAL SUBTYPES OF CERVICAL CARCINOMA IN THE EASTERN U.S.

Family history	Controls *n*	Adenocarcinoma			Squamous		
		n	OR	95% CI	*n*	OR	95% CI
No family history of cervical cancer in a first-degree relative	290	115	1.0		122		
Family history of cervical cancer in a first-degree relative							
Mother	7	5	1.8	0.56–5.8	7	2.4	0.82–6.9
Sister	3	1	0.84	0.09–8.2	3	2.4	0.47–12
Daughter	1	0			1	2.4	0.15–38
Oncogenic HPV(+) controls[2]							
No family history of cervical cancer in a first-degree relative	31	115	1.0		122	1.0	
Family history of cervical cancer in a first-degree relative	2	5	0.67	0.13–3.6	11	1.4	0.29–6.6
Women 35 years or younger							
No family history of cervical cancer in a first-degree relative	122	46	1.0		54	1.0	
Family history of cervical cancer in a first-degree relative	3	2	1.8	0.29–10	4	3.0	0.65–14
Women older than 35							
No family history of cervical cancer in a first-degree relative	168	69	1.0		68	1.0	
Family history of cervical cancer in a first-degree relative	7	3	1.0	0.26–4.1	7	2.5	0.84–7.3

[1]Results from the multicentric study in the Eastern United States.–[2]Defined based on DNA positivity, as defined in the Methods.

first-degree relatives was specifically evaluated (OR = 2.6; 95% CI = 1.1–6.4). For adenocarcinoma, the strongest association was observed when a family history of gynecological tumors other than cervical cancer was evaluated, although this association was not statistically significant (OR = 1.8; 95% CI = 0.67–4.9). Among adenocarcinoma cases, the distribution of non-cervical gynecological cancers reported among first-degree relatives was as follows: 5 women reported a history of uterine cancer (not otherwise specified) and 2 women reported a history of ovarian cancer. A family history of uterine cancer among a first-degree relative was associated with a non-significant elevation in risk of adenocarcinoma (OR = 1.6; 95% CI = 0.47–5.2) and a non-significant reduction in risk of SCC (OR = 0.43; 95 CI = 0.09–2.2).

In analyses that paralleled those carried out in our Costa Rican study, we evaluated risk of SCC and adenocarcinoma associated with a history of cervical cancer among a mother, sister or daughter, and stratified by HPV and age (Table III). For SCC, equivalent elevations in risk were observed regardless of whether history of cervical cancer was reported among a mother, sister or daughter (OR = 2.4). Risk was attenuated in the analysis restricted to HPV positive controls (OR = 1.4; 95% CI = 0.29–6.6). In the analysis stratified by age, comparable effects were observed among women $\leq$35 years (OR = 3.0; 95% CI = 0.65–14) and those >35 years (OR = 2.5; 95% CI = 0.84–7.3; *p* for heterogeneity between young and old = 0.86). In addition, risk was strongest in the analysis restricted to invasive SCC (OR = 3.3; 95% CI = 1.3–8.5), compared to the analysis restricted to *in situ* cases (OR = 1.3; 95% CI = 0.28–6.2), although the difference observed between the 2 groups did not reach statistical significance (*p* for heterogeneity between invasive and *in situ* = 0.25). For adenocarcinoma, no striking findings were noted (Table III). Because a suggestion of elevation in risk of adenocarcinoma was observed among those who reported a family history of uterine tumors in a first-degree relative, we attempted to evaluate whether this effect was strengthened in an analysis restricted to *in situ* or invasive adenocarcinoma cases, or in an analysis restricted to women $\leq$35 years *vs.* >35 years. No evidence for such strengthening was observed within the evaluable strata (data not shown).

No significant differences were noted in the age at diagnosis of *in situ* or invasive SCC or adenocarcinoma cases with or without a positive family history of cervical cancer. The median ages of invasive SCC cases with and without a family history were 42 years and 40 years, respectively (*p* = 0.35). The median ages of *in situ* SCC cases with and without a family history were 25.5 years and 35 years, respectively (*p* = 0.06). Median ages of invasive adenocarcinoma cases with and without a family history were 46 years and 42 years, respectively (*p* = 1.0). There were no *in situ* adenocarcinoma cases who reported a positive family history of cervical cancer.

Discussion

Results from our 2 studies conducted in Costa Rica and the United States suggest that a family history of cervical cancer in first-degree relatives is associated with increased risk of CIN3 and invasive SCC of the cervix. Such an association was not as clearly evident for adenocarcinomas of the cervix, supporting previous assertions that these 2 histological forms of cervical cancer, while sharing HPV infection as a common etiological agent, have different etiologic co-factors.[10] Although numbers were limiting, the association observed between a family history of cervical cancer and CIN3/SCC seemed evident regardless of whether the affected relative was a mother, sister or daughter. Furthermore, the effect did not seem to be strongly modified by age. The fact that the association in our Costa Rican study persisted in analyses restricted to women known to be exposed to oncogenic types of HPV reassures us that the association is not explained by shared environmental risk of viral exposure among relatives. It is unclear why the risk estimate was attenuated in our Eastern United States study in analyses restricted to oncogenic HPV positives, although the small number of controls positive for HPV DNA might have led to unstable risk estimates. One might also speculate that the observed attenuation is due to overmatching in our HPV-restricted analysis. Because the median age of our controls in the Eastern United States study was close to 40 years (as compared to 35 for the Costa Rican study), HPV DNA positive controls in our study may be over-represented by women with persistent HPV infections. If this is the case, and if familial risk observed in our studies is due to genetic factors associated with viral handling, attenuation in risk when comparing cases to HPV positive controls would not be unexpected.

Limitations of the present studies should be mentioned. First, the modest size of our 2 studies combined with the low frequency with which a positive family history was reported resulted in limited power. Despite this limitation, however, significant family history effects were identified in both studies. A second limitation of our studies was reliance on self-reported family history information. This likely resulted in misclassification of family history in both studies. In fact, evidence of misclassification was observed when we re-contacted women in our Costa Rican study to obtain additional details on their pedigrees and family history of cancer (Visit 3). Of the 72 women contacted, the initial report of a positive family history could not be verified in 5 cases (6.9%). It should be noted, however, that in all 5 instances where this occurred, the participant had a diagnosis of <CIN3 (4 controls and 1 CIN2 case), providing some reassurance that any existing misclassification might have biased our estimates of risk toward rather than away from the null.

Some limitations were specific to one of the 2 studies. In the Eastern United States study, for example, there is the possibility

of recall bias among cases, because the questionnaire was administered to women who were aware of their case *vs*. control status. One would expect recall bias to result in similar patterns of risk for both SCC and adenocarcinoma. The fact that the association between a family history of cervical cancer and risk of disease was observed for SCC but not adenocarcinoma suggests that recall bias alone cannot account for our findings. The positive findings observed from our study in Costa Rica, where interviews were conducted before participants were aware of their disease status, further reassures us that recall bias is not an explanatory factor for the observed associations. Also specific to the Eastern United States study is the possibility that the low participation rates might have affected our risk estimates. If cases with a positive family history were more likely to participate than those without, it is possible that our results were biased away from the null. Finally, the control group from our Costa Rican study was selected largely from a colposcopy clinic population and might not have been representative of the entire population with respect to family history of gynecological cancers. Comparison of controls in our study against women in our cohort who were not referred to colposcopy, however, suggested that the largest difference between the 2 groups was the higher oncogenic HPV prevalence among women sent to colposcopy. One might infer from this finding that women in our control group were more likely to have persistent HPV infection than women from the general population. If genetic factors associated with cervical cancer pathogenesis operate through their modulation of host immune or other responses to HPV, having included as controls for our study a group of women with increased prevalence of persistent HPV is likely to have biased our risk estimate associated with family history closer to the null.

Finally, given the nature of familial aggregation studies, we cannot directly determine from our data whether the associations observed for family history are due to genetic or shared environmental factors. Taken in conjunction with other published findings from the literature which have shown (*i*) stronger familial effects among biological relatives compared to half-sisters and adoptive relatives,[7] and (*ii*) consistent evidence for an association between human leukocyte antigen (HLA) polymorphisms and risk of cervical cancer,[8] our findings suggest the likelihood that genetic susceptibility does play a role in cervical cancer pathogenesis.

Strengths of our studies should also be mentioned. First, the Costa Rican study is a population-based study with high participation rates. The fact that questions regarding family history were administered before participants were aware of their disease status limits the possibility of recall bias in that study. The Eastern United States study is the largest study to date to evaluate the association between family history of cancers and risk of cervical adenocarcinomas. The ability to evaluate the association between family history and disease in 2 very distinct populations in Costa Rica and the United States is another strength of the present analysis. Finally, we were able to account for HPV infection in both studies, and in the Costa Rican study were able to do so using both measures of current (DNA-based) and past (serology-based) infections.

Results from our 2 studies provide the basis for future efforts to more directly evaluate the role of genetic susceptibility as a determinant of risk of cervical cancer and its precursors. Future efforts to evaluate the role of inherited genetic factors, including those that might modulate host responses to HPV infection, might provide important clues into the pathogenesis of cervical cancer and other tumors associated with common DNA viruses.

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